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**PATENT**

Case Docket No. IMEC299.001AUS
Date: May 18, 2004

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant(s) | : | Wirix-Speetjens, Roel |
| Appl. No. | : | 10/810,048 |
| Filed | : | March 26, 2004 |
| For | : | METHOD FOR THE CONTROLLED TRANSPORT OF MAGNETIC BEADS AND DEVICE FOR EXECUTING SAID METHOD |
| Examiner | : | Unassigned |
| Group Art Unit | : | Unassigned |

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## TRANSMITTAL LETTER

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(X) Certified Priority Document for European Patent Application having application number 03447072.4, filed March 28, 2003.

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

**Patentanmeldung Nr. | Patent application No. | Demande de brevet n°**

03447072.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

**R C van Dijk**

Anmeldung Nr:
Application no.: 03447072.4
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Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Method for the controlled transport of magnetic beads and devices for the method

In Anspruch genommene Prioriät(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
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# Method for the controlled transport of magnetic beads and devices for the method.

## Field of the invention

The present invention is related to the field of microelectronic devices, designed to transport and manipulate magnetic beads on chip. Application domains are biochips, biosensors, diagnostics, genetics and molecular studies.

## Background of the invention

Following the publication of the first draft of the human genome sequence, the next major task is to determine the function that each of the genes (i.e. > 35,000) have in each of the tissues in the body over a range of environmental conditions. Using arrays of thousands of probes which are specific to individual genes, DNA microarrays enable the extent to which individual genes are switched on or off to be determined. Genetic variation among individuals also contributes to variation in the way genes behave in response to changes in the environment. Simultaneous detection of variation at thousands of locations (i.e. single nucleotide polymorphisms or SNPs) in the genome can also be achieved using DNA microarray technology. Applications of DNA microarrays therefore include gene expression profiling, gene sequencing, gene discovery, and genotyping, for users in healthcare, academia and the pharmaceutical and biotechnology industries. Currently the major factors limiting the uptake of DNA microarray technology include low sensitivity, the high cost of the technology, requirement for specialist operators and throughput.

Electronic biochips have the potential to overcome these limitations. Here, exploitation of state-of-the-art micro- and nano-technology design, fabrication and characterization tools and processes enable development of devices and systems that can interface directly with biological reactions. A possibility involves combining magnetic bead-based bioassays with magnetic sensor technology. From a biotechnology perspective, paramagnetic beads (0.05-10.0μm diameter) are available commercially from a number of sources with a range of surface functionalisation chemistries, for well established applications including isolation and transportation of nucleic acids, proteins and whole cells. In microelectronics, GMR-based magnetic sensors have provided an enabling technology for memory applications. Thus, integration of paramagnetic bead-based nucleic acid assays on a functionalised biochip surface incorporating magnetic sensors, provides the basis for a range of biochip platforms.

Next to the detection of the magnetic beads, the transport and manipulation of beads is a limiting factor which has to be taken into account in biochip designs and methods.

In the past systems have been described for the manipulation of magnetic microbeads based on permanent or electromagnets with dimensions >5mm, which did not allow for magnetic fields localised over microscale regions. Commercial devices exist for sorting and separation of magnetic microbeads, but they have a limited capability of performing complex manipulations of these beads since they make use of permanent magnets or electromagnets.

In Whitesides et al., "Manipulation of magnetic microbeads in suspension using micromagnetic systems fabricated with

soft lithography", Applied Physics Letters [Vol 78, Nr 12 March 19th 2001, pages 1775-1777] and US2002/0166800, systems are described comprising current carrying wires that can generate strong local magnetic field gradients, which in their turn can control de position of magnetic microbeads in aqueous suspension.

**Aim of the invention**

It is an aim of the invention to provide a novel method and corresponding devices for the manipulation and transportation of magnetic beads on chip. The invention mainly points to application in the domain of biochips and microarrays, used in diagnostics, genetics and molecular studies.

**Summary of the invention**

A method for the controlled transport of magnetic beads between a position X and different position Y is disclosed, wherein the magnetic beads are manipulated or transported by applying successively a series of N local magnetic fields which have magnetic field gradients different from 0 in the neighbourhood of the magnetic beads.

Magnetic beads are known in the art and can have sizes between 50nm and 10$\mu$m. Preferably the magnetic beads have sizes between 100nm and 5 $\mu$m. Preferably the magnetic beads are suspended in a fluid.

For the purpose of this invention the term 'local magnetic field' should be understood as the magnetic field which is essentially felt by the magnetic bead. Technically other magnetic fields can be generated at the same time when the local magnetic field is generated, but then they have to be sufficiently spatially separated from the bead. Possibly at least one of these contemporary fields may become a local

magnetic field later in the controlled transport process according to the present invention.

In preferred embodiments aimed at the application areas of biochips, biotechnology, diagnostics, genetics and molecular studies the magnetic beads are attached to biological or chemical specimen. Also possible is that magnetic or chemical specimen already carry a magnetic moment and coupling to a magnetic bead is not anymore necessary; seen in another way, the biological or chemical specimen can have an integrated magnetic bead.

Preferably the local magnetic field is essentially spread over an area which has dimensions of the order of 5 to 50 times the size of the bead or group of beads. More preferably the local magnetic field is essentially spread over an area which has dimensions of the order of 10 to 40 times the size of the bead or group of beads. A group of beads localised at a location of minimal energy in a magnetic field can have different spatial distributions, induced by the shape of the field. An indicative but not necessarily precise measure for the size of a group of beads can be the distance between the begin and the end of the group, measured along the current direction.

Preferably the application of the local magnetic field is long enough to allow the magnetic bead to move to the location of its lowest energy in the local magnetic field (L_E_min). Embodiments wherein the time of application of the local magnetic field is shorter then the time necessary to allow the magnetic bead to move to the location of its lowest energy in the local magnetic field are also possible, but at the moment of switching to the next local magnetic field, the bead must in that case have reached the influence area of the next local magnetic field such that it is attracted towards the location of its lowest energy in this next local magnetic field.

An aspect of the present invention is that each of the local magnetic fields, which have a gradient different from 0 in the neighbourhood of said magnetic bead, is generated by a single current carrying structure.

These current carrying structures can be created by standard state-of-the-art microelectronic process technology.

The series of N successive local magnetic fields can generated by M current carrying structures.

Each of these current carrying structures has a non constant charge current density in order to achieve a gradient different from 0 in the neighbourhood of said magnetic bead.

The non-constant charge current density can be generated by varying the shape of the cross-section of the current carrying structure.

The non-constant charge current density can be generated by varying the cross-section surface area of the current carrying structure.

The non-constant charge current density can be generated by varying the width of the current carrying structure along the current direction.

The series of N locations of lowest energy (L_E_min {i}, with i between 1 and N) of the magnetic beads, corresponding to the series of N local magnetic fields, defines a predefined path.

In a preferred embodiment M equals 2 and the local magnetic fields are generated alternatingly in each of the current conducting structures.

Preferably current carrying structures have a periodic shape, formed by repeating a basic structure element.

Preferably this basic structure element has no mirror symmetry with respect to an axis which is orthogonal to the current direction.

Preferably the cross-section surface area is decreasing when going from 1 side of the basic structure element to the other side of the basic structure element, along the current direction.

In a preferred embodiment the current carrying structures are isometric.

In a preferred embodiment the current carrying structures are positioned above eachother, being shifted over a distance different from 0 along the current direction.

In another preferred embodiment the current carrying structures are positioned next to eachother such that their respective current directions are parallel and wherein both structures are shifted over a distance different from 0 along the parallel direction.

Advantageously the shifted distance equals half the length of the basic structure element.

In a preferred embodiment the basic structure element is sharkfin-like or triangular-like.

The method according to the present invention can be used in detection schemes for biological or chemical specimen, wherein the controlled transport of biological or chemical specimen is important.

The method according to the present invention can be applied on a cluster or group of magnetic beads, whereby isolation, alignment and sequencing of magnetic beads is achieved due to the limited spatial resolution of the predetermined path compared to the bead size. These properties can be advantageously used in lab on chip design and analysis methods. They allow for instance the bead per bead - and consequently per one biological or chemical specimen based transport or manipulation.

## Detailed description of preferred embodiments

Movement of magnetic beads in a 1-dimensional way is achieved by applying a magnetic force:

$$\vec{F} = \mu_0 \vec{M} \cdot \vec{\nabla} \vec{H}$$

Such a magnetic force can thus be generated by both magnetizing the super-paramagnetic bead and creating a magnetic field gradient. On-chip field generation lines can create both. Figure 1a-b (can be fabricated using 2 metallisation steps) and Fig. 1c-d (can be fabricated using a single metallisation step) show structures that are able to form a magnetic field gradient and hence are able to pull a magnetic bead towards the smallest width of the conductor or current carrying structure. Pictures of the corresponding real examples are depicted in Fig. 3 and 4. As can be derived from Fig. 2a-b (basic elementary structure corresponding to a length of 20 $\mu$m and a width of 20 $\mu$m) and Fig. 2c-d (basic elementary structure corresponding to a length of 40 $\mu$m and a width of 20 $\mu$m), the structures can be characterised in that they generate a magnetic field gradient different from 0 because their current density within each basic structure element is not constant. These structures have a periodically repeating basic structural element. In this case the basic structural element is sharkfin-like, but this can also be triangular (double-sharkfin) or can have other shapes. By shifting a second conductor half a period from the first, magnetic beads can be moved in a peristaltic way from one minimal width to another. This occurs by switching alternating DC currents through the conductors. For the given examples of current carrying structures a magnetic bead size of the order of 2 $\mu$m can be preferred.

Preferably both conductors behave magnetically in a similar way. In order to do this, a first metallization [TiW (10nm) / Au (150nm) / TiW (10nm)] can be deposited on the substrate, which can be followed by a passivation layer Si3N4 [500nm]. To start with a flat surface, a CMP step flattens the topography, keeping a certain thickness of the Si3N4 to isolate both conductors. The second metallization can be deposited in exactly the same way as the previous one, again followed by a passivation layer. In this way, both conductors have the same current distribution and hence the same magnetic behavior. Other planarization steps, such as SOG or damascene process technology can replace the CMP step.

To increase the force on a magnetic bead, one can deposit a flux-guiding material underneath the first conductor. In this way, the generated magnetic field -and hence the magnetic force- can be doubled on top of the conductor. This can either increase the magnetic force on a magnetic bead or either decrease the current through the conductor and in this way, lower the heating (Joule) effect.

Both the current and the shape of the conductor will determine the switching speed and hence the overall speed of the (ensemble of) magnetic bead(s).

Fig. 5 shows simulation results that illustrate the relation between the average speed of the bead and the current in the current carrying structure for different values of the width of the basic structure element. Results are plotted for basic structural elements with widths of 20, 30 and 40$\mu$m, for a length of 60$\mu$m and a thickness of 6 $\mu$m.

Fig. 6 shows simulation results that illustrate the relation between the average speed of the bead and the current in the current carrying structure for different values of respectively the length of the basic structure

element. Results are plotted for basic structural elements with lengths of 10, 40, 60 and 100μm, for a width of 20μm and a thickness of 6 μm.

Typical currents can be between 10 and 100mA, but higher or lower currents are not excluded.

**Description of Figures**

Fig. 1a and 1b illustrate a preferred embodiment of the present invention for which the fabrication comprises 2 metallization steps ((1)+(2)). Fig. 1c and 1d illustrate a preferred embodiment of the present invention for which the fabrication comprises 1 metallization step. Fig. 1a and 1c are top views. Fig. 1b and 1d are cut-views along respectively the lines B-B′ and C-C′.

Fig. 2b and 2d illustrate 2 current carrying structures according to an embodiment of the current invention, wherein the 2 current carrying structures differ by a difference in the length (A-A′, B-B′) of the basic structure element.

Fig. 2a and Fig. 2c are showing the evolution of the current density in function of the longitudinal position in the basic structure element.

Fig. 3 is a picture of a practical realisation of a preferred embodiment of the present invention, corresponding to Fig 1a.

Fig. 4 is a picture of a practical realisation of a preferred embodiment of the present invention, corresponding to Fig 1c.

Fig. 5 shows simulation results that illustrate the relation between the average speed of the bead and the current in the current carrying structure according to a preferred embodiment of the present invention, for different values of the width of the basic structure element.

Fig. 6 shows simulation results that illustrate the relation between the average speed of the bead and the current in the current carrying structure according to a preferred embodiment of the present invention, for different values of the length of the basic structure element.

**Claims**

1. A method for the controlled transport of magnetic beads between a position X and different position Y, wherein said magnetic beads are manipulated or transported by applying successively a series of N local magnetic fields which have magnetic field gradients different from 0 in the neighbourhood of said magnetic beads.

2. Method according to claim 1, wherein said magnetic beads are attached to biological or chemical specimen.

3. Method according to claim 1 to 2, wherein each said local magnetic field is essentially spread over an area which has dimensions of the order of 5 to 50 times the size of the bead or group of beads.

4. Method according to claim 1 to 3, wherein the application of said local magnetic field is long enough to allow said magnetic bead to move to the location of its lowest energy in said local magnetic field (L_E_min).

5. Method according to claim 1 to 4, wherein each said local magnetic field is generated by a single current carrying structure.

6. Method according to claim 5, wherein said current carrying structures are disposed on a substrate by microelectronic process technology.

7. Method according to claim 1 to 6, wherein said series of N successive local magnetic fields is generated by M current carrying structures.

8. Method according to claim 5 to 7, wherein each said current carrying structure has a non-constant charge current density.

9. Method according to claim 8, wherein said non-constant charge current density is generated by

varying the shape of the cross-section of said current carrying structure.

10. Method according to claim 9, wherein said non-constant charge current density is generated by varying the cross-section surface area of said current carrying structure.

11. Method according to claim 9, wherein said non-constant charge current density is generated by varying the width of said current carrying structure along the current direction.

12. Method according to claim 1 to 11, wherein the series of N said locations of lowest energy (L_E_min {i}) of said magnetic beads, corresponding to said series of N local magnetic fields, defines a predefined path.

13. Method according to claim 1 to 12, wherein M is 2 and where said local magnetic fields are generated alternatingly in each of the current conducting structures.

14. Method according to claim 13 whereby current carrying structures have a periodic shape, formed by repeating a basic structure element.

15. Method according to claim 14, wherein said basic structure element has no mirror symmetry with respect to an axis which is orthogonal to the current direction.

16. Method according to claim 13 to 15, wherein said cross-section surface area is decreasing when going from 1 side of said basic structure elements to the other side of said basic structure element, along the current direction.

17. Method according to claim 13 to 16 wherein both said current carrying structures are isometric.

18. Method according to claim 17, wherein said current carrying structures are positioned above eachother, being shifted over a distance different from 0 along the current direction.

19. Method according to claim 17, wherein said current carrying structures are positioned next to eachother such that their respective current directions are parallel and wherein both structures are shifted over a distance different from 0 along the parallel direction.

20. Method according to claim 18 to 19, wherein said distance equals half the length of said basic structure element.

21. Method according to claim 14 to 20, wherein said basic structure element is sharkfin-like or triangular-like.

22. Method according to claim 1 to 21, applied on a cluster of magnetic beads, whereby isolation, alignment and sequencing of magnetic beads is achieved due to the limited spacial resolution of said predetermined path compared to the bead size.

23. A method for the detection of said biological or chemical specimen, wherein the method according to claim 1 to 22 is used as a transport mechanism for said biological or chemical specimen.

24. Device according to the method of claim 1 to 22 for the controlled transport of magnetic beads.

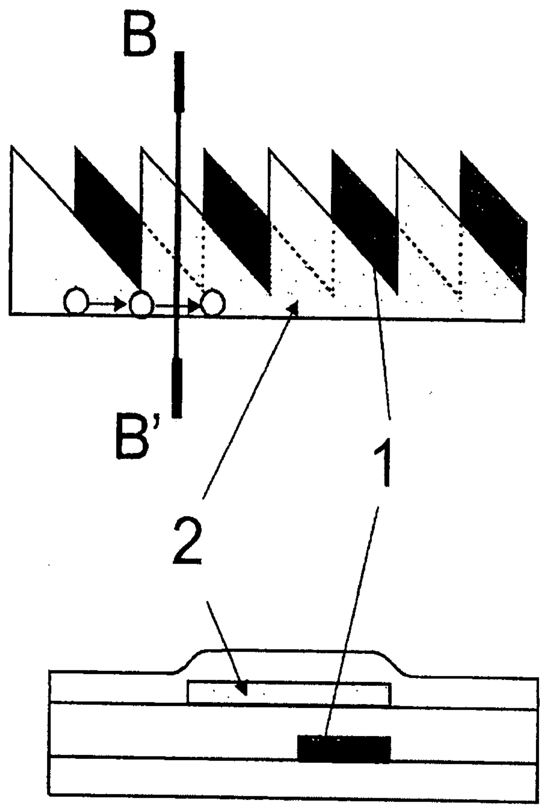
## Abstract


**Method for the controlled transport of magnetic beads and devices for the method.**

The present invention is related to a method for controlled transport of magnetic beads between a position X and different position Y, wherein said magnetic beads are manipulated or transported by applying successively a series of N local magnetic fields which have magnetic field gradients different from 0 in the neighbourhood of said magnetic beads. Each of these N local magnetic fields is generated by a single current carrying structure, in which the current density is not constant. The invention mainly points to application in the domain of biochips and microarrays, used in diagnostics, genetics and molecular studies.

FIG. 1

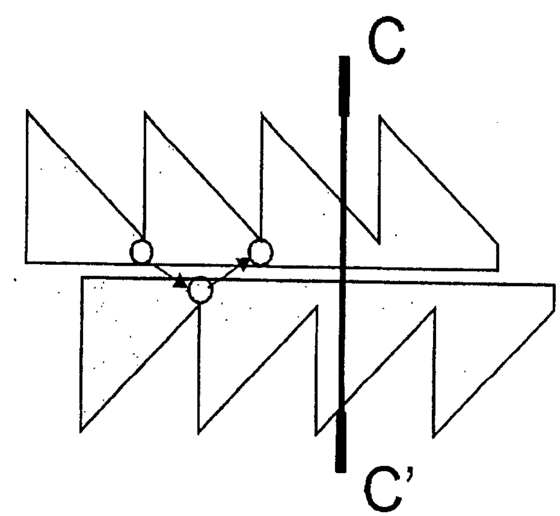
Fig. 1a

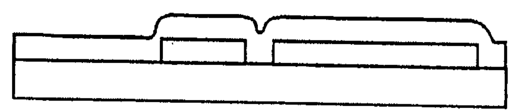



B-B'

Fig. 1b

Fig. 1c



C-C'

Fig. 1d

Fig. 2a

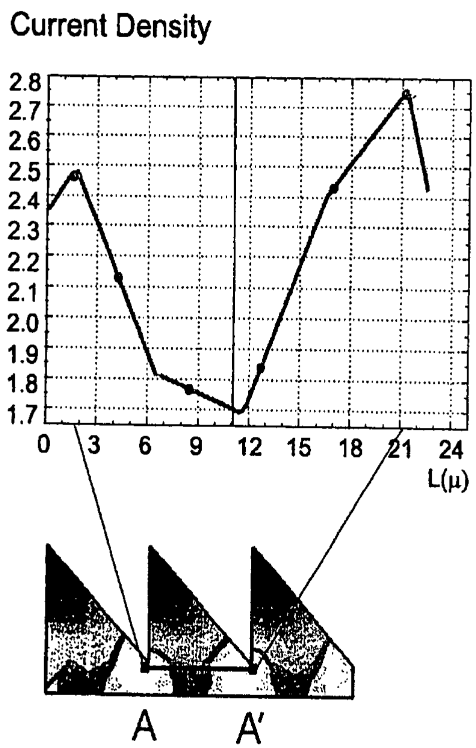



Fig. 2b

Fig. 2c

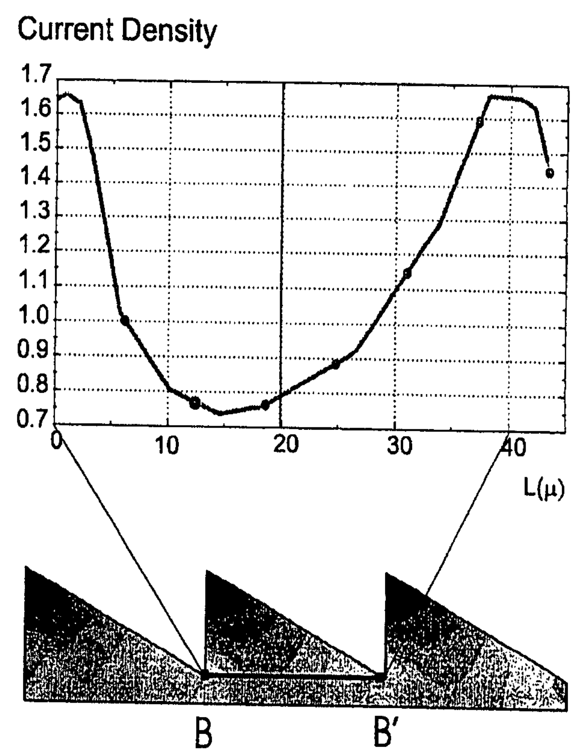



Fig. 2d

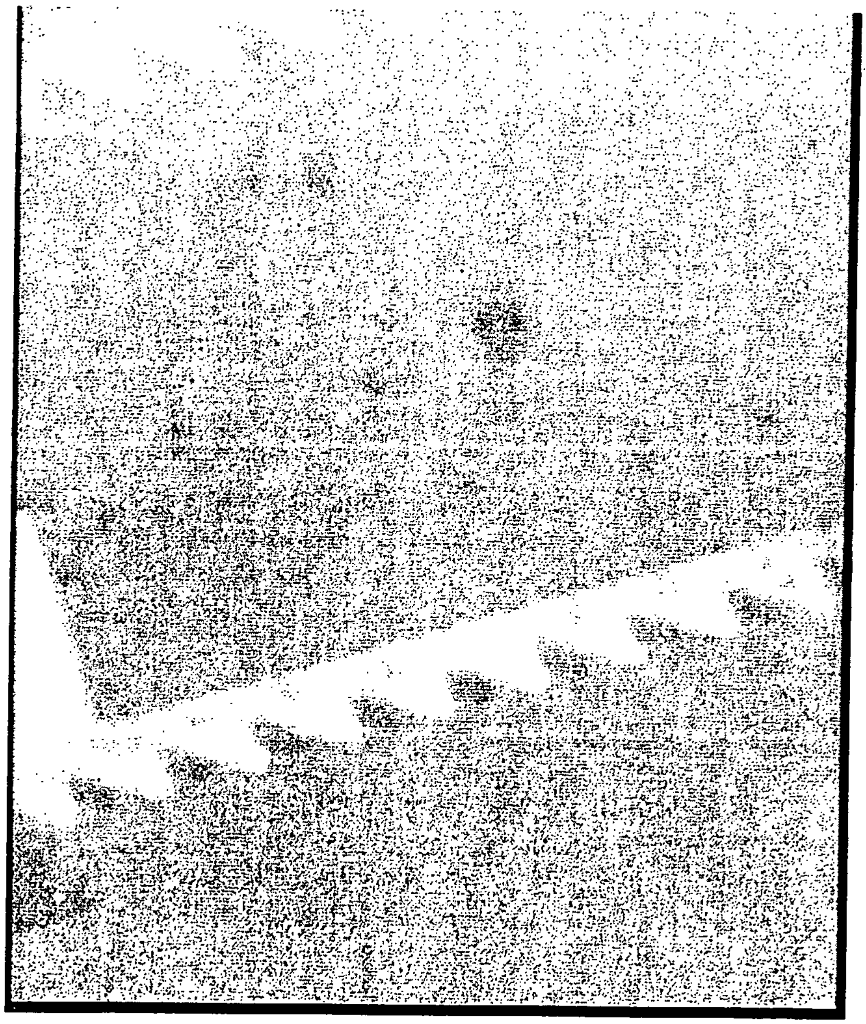


Fig. 3

Fig. 4

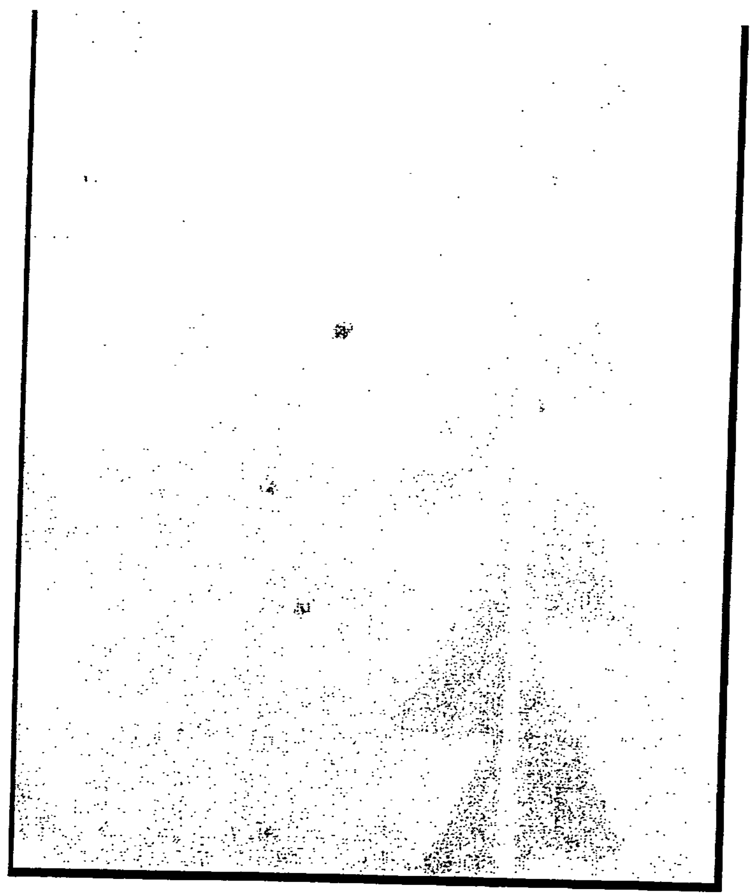
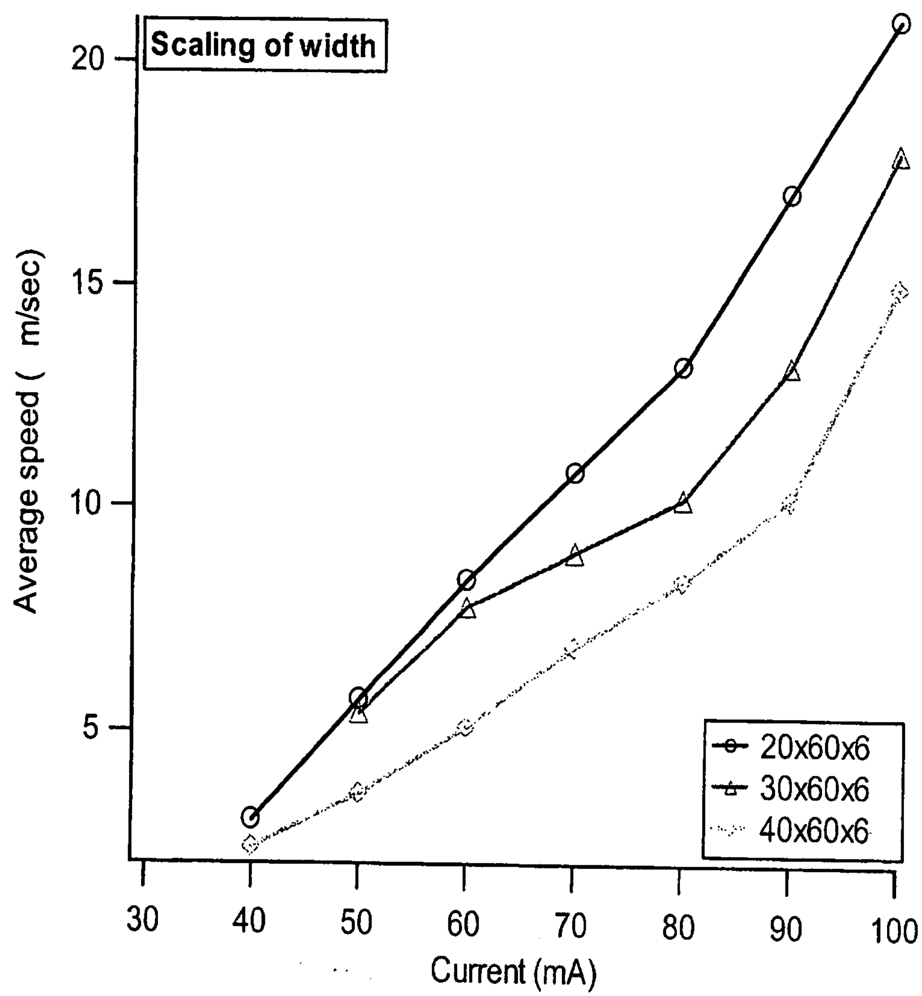


Fig. 5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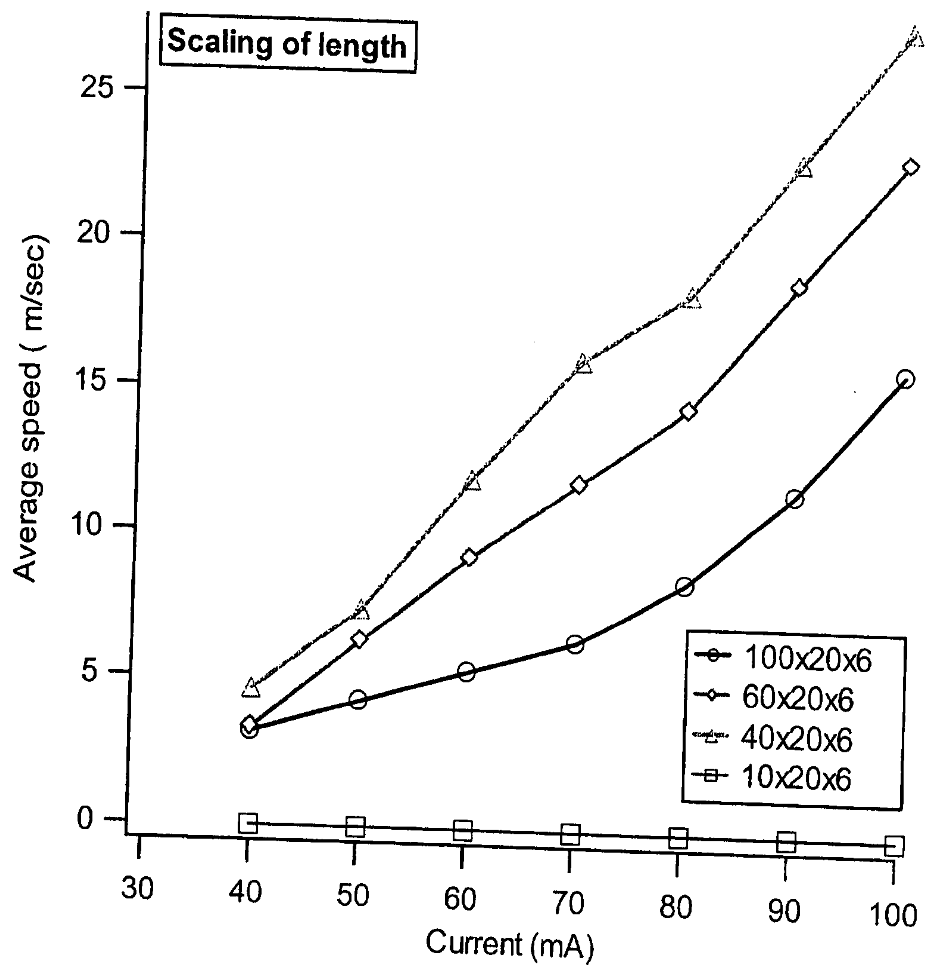
20
15
10
5
30
40
50
60
70
80
90
100
Current (mA)
20x60x6
30x60x6
40x60x6

Fig. 6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Current (mA)
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60x20x6
40x20x6
10x20x6